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Information on the mental status of Soldiers is vital to their management in future deployments to prevent acute performance deficits and post-deployment health consequences such as chronic multisymptom illnesses and neurodegenerative diseases. The military needs a parsimonious set of reliable neuropsychological tests that: (1) provide early detection of individual impairment and (2) predict occupational and deployment health risks. Testing must characterize cognitive lapses and mood changes in healthy individuals faced with relevant operational stressors, including chemical exposures and interactions with other stressors, and should be based on understanding effects of final common pathways in brain physiology (e.g. hypo- or hyperglycemia, and hypoxia, oxidative stress, and inflammation). Stressors may affect a common hierarchy of deficits and batteries could be reduced to a few tests such as simple reaction time, matchin-to-sample, running memory, math processing, and code substitution; alternatively, these tests together might provide a differential diagnosis. The ultimate goal of unobtrusive real-time mental status monitoring may one day provide the most sensitive indication of a neurochemical exposure.

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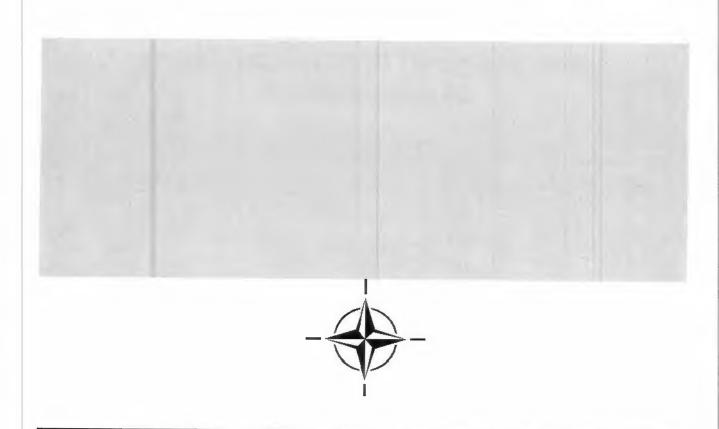ORGANISATION

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BIOTECHNOLOGIES FOR ASSESSMENT OF TOXIC HAZARDS IN OPERATIONAL ENVIRONMENTS

BIOTECHNOLOGIES FOR ASSESSMENT OF TOXIC HAZARDS IN OPERATIONAL ENVIRONMENTS

Executive Summary

This group focused on markers of exposure for assessment of neurotoxicological threats from non-threat agents. Starting with reviews of standard approaches to toxic industrial chemicals and toxic industrial materials (TIC/TIMs), this group considered the specialized health risks to deployed military forces arising from exposure to toxic hazards chemicals that usually involve mixtures and interactions with other stressors and conditions. To narrow the discussion, two model systems were evaluated in detail, permethrin and JP8. These compounds represent militarily relevant chemical mixtures that are inhalation and dermal exposure hazards with neurotoxicological potential. Participating countries had various contributions to new research, evaluation, and discussion of approaches to assessing health and performance risks of these two categories of chemicals, ranging from neurobehavioral to special in vitro exposure test systems and cellular biomarkers. Interactions with physical factors (e.g., heat, dust, work/exercise), psychological stress, and other chemical exposures were evaluated. Communicating health risks to military forces to improve protective measures is itself a potential health risk and requires additional specialized research to establish rules of communication to achieve optimal compliance with safety and protective measures and minimal reductions. Two international EIHH workshops paralleled the efforts of this panel and expanded contributions to this work. Further work in these areas is being conducted with agreements to continue sharing of information on different approaches to assessing neurotoxicological risks. Recommendations were made for NATO and national implementation involving further development of efficient processes for early predeployment consideration of potential threats, assessment and monitoring of neurochemical hazards, and lifecycle health monitoring of exposed individuals.

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Chapter 6 – Neurobehavioral Toxicity Assessments

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6.1 ABSTRACT

Information on the mental status of Soldiers is vital to their management in future deployments to prevent acute performance deficits and post-deployment health consequences such as chronic multisymptom illnesses and neurodegenerative diseases. The military needs a parsimonious set of reliable neuropsychological tests that: (1) provide early detection of individual impairment and (2) predict occupational and deployment health risks. Testing must characterize cognitive lapses and mood changes in healthy individuals faced with relevant operational stressors, including chemical exposures and interactions with other stressors, and should be based on understanding effects of final common pathways in brain physiology (e.g., hypo- or hyperglycemia, and hypoxia, oxidative stress, and inflammation). Stressors may affect a common hierarchy of deficits and batteries could be reduced to a few tests such as simple reaction time, matching-to-sample, running memory, math processing, and code substitution; alternatively, these tests together might provide a differential diagnosis. The ultimate goal of unobtrusive real-time mental status monitoring may one day provide the most sensitive indication of a neurochemical exposure.

6.2 INTRODUCTION

The Soldier is the acknowledged centerpiece of the Army's warfighting system, and military success will largely depend on the mental status of these individuals. The complexity, speed, and lethality of modern warfare means that even small mental lapses may have catastrophic consequences. Judgment and other forms of decision-making, mood and cooperation, psychomotor performance, and cognitive status are all critical elements of Soldier performance. In the military, these elements have been traditionally evaluated by observation or, after the fact, as net outcomes such as task or mission completion. Thus, rigorously specified neuropsychological testing methods are needed to fill a vital technological gap in Soldier health and performance research [1, 2]. A very important part of this effort is to explore the neuropsychological methods in militarily relevant conditions to extend our understanding of relevant functional domains and how well they correspond to modes of testing. The Automated Neuropsychological Assessment Metric (ANAM) was started by Dr. Fred Hegge as a means to provide standardized and valid testing for a wide variety of military applications [3, 4]. The intent is to serve as a plug-and-play toolkit of tests for research and for practical application (Table I). This paper discusses the military research needs for ANAM test batteries in terms of neurotoxicity assessments and relevant neurophysiological studies.

Table I. Potential Military Applications of ANAM

Objective	Examples of Potential Applications
Health Applications • Baseline status of new recruits • Periodic health status assessment • Occupational hazards monitoring • Post-deployment health monitoring • Safety evaluations of new materiel	• Recruit Assessment • Comprehensive Health Care System II (CHCSII) • Preventive medicine investigative tool Program (RAP) • Early diagnostic tool in redeployment screening • FDA-approved testing standard
Performance Applications • Fitness for duty and return-to-duty status • Real-time soldier status monitoring • Human factors evaluations of new materiel and combat concepts	 • Pre-mission screening tool • Embedded task testing in future systems • MANPRINT

6.3 APPLICATIONS OF NEUROPSYCHOLOGICAL TESTING

6.3.1 Health Assessments

Currently there is no practical method to establish the baseline mental status of new recruits. The only information recorded that may help in the evaluation of future neurotoxicity issues is from the conventional medical history and general aptitude testing from the Armed Forces Qualification Test. A new initiative to collect more detailed health and psychological status within the first week of military service, the Recruit Assessment Program (RAP), still only provides self-report questionnaire data [5]. An efficient session, and possibly repeat sessions, with a brief ANAM test battery might provide exceptionally valuable information. This test battery would have to be well validated for reliability and reproducibility and, most importantly, demonstrate value in detecting meaningful changes in health and performance status for early disease states or non-obvious changes in militarily relevant performance that might be traceable to chemical exposures. These dangers could be resolved sooner if a sensitive test methodology for early detection existed. A key platform for this future standardized testing and data repository would be the Comprehensive Health

Care System II (CHCSII) database [6].

6.3.2 Readiness Status Assessments

Taken a step further into the future, periodic neuropsychological testing of all military members might be invaluable to readiness status assessments, early identification of illness, and detection of unanticipated occupational or deployment health risks. This would provide an opportunity to detect neurotoxic influences and other neurological susceptibilities in individuals before deployment. Currently, the Army conducts physical fitness testing and weighs all members twice a year to ensure individual physical readiness. In a technologically sophisticated future force, it will be important to commit at least equal emphasis on cognitive readiness, perhaps including Nintendo-like game tests or timed puzzle-solving challenges that will have been derived from current investigations using automated neuropsychological testing. Like remedial physical training for those not meeting physical fitness criteria, further evaluation and remedial training to build cognitive resilience or neurophysiologically-based skills could be developed. This new emphasis on cognitive readiness will likely converge with physical training standards as we learn more through new Army research initiatives on the neurobiology of exercise and neuropsychological testing in physically active Soldiers.

6.3.3 Materiel Safety Evaluations

Materiel safety evaluations require a well-standardized test methodology. The tests in such a battery must have clearly demonstrated thresholds or definitions of impaired neuropsychological performance. This test capability (i.e., norms and thresholds) is important for generation of valid test data to support approval of new drugs and other medical materiel. The Army needs to go a step beyond traditional FDA approvals, to include testing of new products in operationally relevant environments to ensure that there are no important interactions between the product and key operational stressors. Under the Army's MANPRINT process of new system evaluation, even non-medical materiel concepts that do not require FDA approval are required to consider effects on human health and performance. MANPRINT requires consideration of human factors and medical safety in the design of new equipment at all stages of the development process [7]. Therefore, a relevant test battery that provides valid data in messy field conditions will be especially important. The neurobehavioral testing methods that have been well developed for neurotoxicological assessments [8, 9] provide a strong basis for field investigations of unforeseen interactions, such as the current initiatives to develop these tools using permethrin and JP8, the intended universal military fuel, as the initial focus.

6.3.4 Relevance to Military Performance Outcomes

In addition to standardization and validation of testing methods, research is needed to clarify the measurements that correspond to militarily relevant performance outcomes. This was a key objective of the Office of Military Psychological Assessment Test (OMPAT) program, which initiated development of the ANAM and other electronic testing softwares such as the MicroSaint simulation software to study crew interactions. The OMPAT program was initiated in 1984 to assess the impact of operationally employed drugs on normal performance. The program was funded from the medical chemical defense program, with specific interest in nerve agent prophylaxis. However, the problem continues to defy research attempts.

6.3.5 Performance Assessments

Future Soldier concepts include technologically enabled individuals operating in "net-centric" teams with unprecedented access to information, decision-assist technologies that will suggest solutions to forecasted problems, multi-sensory inputs ranging from tactile feedback to 3-D audio spatial "displays," and

instant fingertip or voice access to unmanned aerial vehicles and other remote robotic weapons and intelligence systems, and other equipment and adornments. The future Soldier will be an extraordinarily powerful and lethal system, and decision-making ability of the human element will be of critical importance. Commanders will demand assurances that Soldiers are mentally fit for duty and may rely on monitoring systems that will indicate when human failure is imminent. The new technologies will add to the neuropsychological burden of the Soldier, but also provide more opportunities to unobtrusively monitor performance status through physiological measures; for example, emotional status estimated from voice stress analysis via existing communications systems [10] to task performance testing embedded in routine check-in and calibration procedures. Reliability of the mental status assessments of the Soldier will be even more important in any applications where the assessment system can automatically take control away from the Soldier in the loop. This concept of machine decision assist is the basis of several current DoD programs that range from balancing workload and decision making between team members based on the cognitive status assessment of each individual to systems that would take away controls of an aircraft if the pilot appears to be impaired, either through physiological measurements or illogical responses [11].

6.3.6 Warfighter Physiological Status Monitoring systems

In some settings, Soldiers may be operating in remote areas away from a main force, or they may be out of sight of their team members during operations in urban terrain, or while fully encapsulated in protective clothing and masks. In these cases, it could be important to have objective information on the cognitive status of an individual or a team which cannot be more directly observed or monitored. Ideally, the monitoring system would involve passive and continuous assessments. This is the concept behind Warfighter Physiological Status Monitoring (WPSM), a system of wear-and-forget non-invasive physiological monitors that will use a combination of sensor signals to determine how a Soldier is doing, when the Soldier has been injured, and when the Soldier is headed for trouble in terms of injury consequences (e.g., overheating, dehydration, overexertion) or in terms of performance lapses (from e.g., toxic chemical exposures, fatigue, psychological stress, information overload) [12]. Predicting impending problems from physiological signals is difficult because of the compensatory mechanisms that sustain an individual in the face of external challenges until compensation is no longer possible (i.e., the distinction between the "amber" warning of impending trouble and the "red alert" when the Soldier is already a casualty). Neuropsychological testing in experimental settings is likewise affected by subjects temporarily rallying to complete a test even when they may be extremely fatigued or challenged in some other way. The earliest form of a WPSM approach to neurocognitive assessments is likely to use extremes of the physiological range of measures such as very low or high blood glucose levels (from minimally invasive sub-dermal probes) and recent sleep history (from wrist-worn accelerometry) to predict likely performance lapses. Whatever system is employed will have been developed against a reference standard of automated neuropsychological testing. It is also likely that for some critical assessments of cognitive status, relatively unobtrusive testing will be built into regularly scheduled tasks or games that Soldiers will perform using computers that every Soldier will be wearing.

6.4 HYPOTHESES CONCERNING OPERATIONAL STRESSORS AND TEST PERFORMANCE

6.4.1 Common brain physiology mechanisms produced by military stressors

The nature of the deficits that occur in various physiological states has not been well mapped. For many key stressors there appears to be a general trend to preserve core survival functions at the cost of higher cortical functions (i.e., loss of function progresses in a rostral-caudal direction), suggesting that for some

applications, a test battery could be devised to specifically test this progression of impairment. This appears to be the case for hypoglycemia, with marked changes in cognitive testing occurring below 3 nmol/L; memory is one of the first tests affected [13]. This is also the case with acute hypoxia, with an average 25% reduction in short-term memory during ascent from sea level to over 14,000 feet altitude, corresponding to a reduction from 96 to 40 torr in arterial partial pressure of oxygen [14]. Likewise, cold exposure (e.g., 1 hour or more at 4°C, or immersion in water at 10°C) produces reductions in match-to-sample testing more consistently and with greater sensitivity than any other neuropsychological test [15, 16]. More remarkable in these tests is the finding that tyrosine ingestion can reverse the deficit [17]. Along with more definitive data from brain microdialysis studies in rats, this suggests that catecholamine synthesis in the brain plays a role and that increased substrate availability may be all it takes to counter deficits that are produced by this mechanism of stress-induced catecholamine reduction [17]. In each of these three stressors (neuroglycopenia, hypoxia, and cold), working memory is one of the first functional axes affected, followed by tests in other domains such as attentiveness. This suggests that for some monitoring applications, relatively simple test batteries could be devised that might provide a generalizable assessment of acute performance status.

6.4.2 Other stressors

6.4.2.1 Chronic psychological stress

Other stressors, especially involving longer exposures (e.g., >24 hours), appear to produce more specific and unique functional deficits. Some of these have been attributed to specific mechanisms such as the link between chronic cortisol exposure, shrinkage of the hippocampal volume, and effects on memory functions [18]. Chronic cortisol exposure could result from a variety of stressors, although chronic anxiety, severe trauma, and other psychological factors are probably the most important.

6.4.2.2 Head impact

Although head impact can be a focal insult affecting a specific region of the brain, concussion has generalized effects on the brain, and Warden, Bleiberg, and colleagues [19, 20] suggested that global speed of processing reflected in a simple reaction time might even provide a practical single test of impairment and return-to-duty status. This is being further investigated in cadet boxing and parachute-landing models in the military, and has already provided pioneering studies in baseline and repeated testing methods.

6.4.2.3 Sleep deprivation

Sleep deprivation and short-term interventions have been well studied by the military. This provides a different model of neuropsychological impairments which may be traceable to observed hypometabolic responses in specific regions of the brain. A greater than 50% reduction in "throughput" (primarily a reduction in speed) on several neuropsychological tests at 48 hours of sleep deprivation is reversible for 4-6 hours with 600 mg of caffeine [21]. Memory tests are not very sensitive to the effects of this stressor, especially compared to tests of attentiveness such as the psychomotor vigilance test (PVT) [22]. The PVT should provide direct comparisons to ANAM tests with other stressors.

6.4.2.4 Commonalities in test outcomes

Related mechanisms involving oxidative stress, inflammation, and excitatory neurotransmitters may be common to many of these other stressors. Regardless of the stressor, there appears to be a common behavioral strategy to handle impairments. In a variety of tests that includes hypoglycemia, concussion, and sleep deprivation, the overall speed of mental processing is typically sacrificed to preserve accuracy [13, 20, 21]. If this rule can be reliably established for certain test applications, an index based on accuracy and speed might form the basis of a measure of mood status and motivation to perform well.

6.4.3 Neurotoxic exposures

Neuropsychological testing relevant to military applications is most advanced in the area of neurotoxicology [8,9,23,24]. Various classes of chemicals have been characterized for their highly specific regional and functional effects. In some cases, neuropsychological effects of heavy metals, solvents, organophosphates, and various agricultural and industrial chemicals provide the primary classification of biological effects, where physiological and anatomical lesions may be much more difficult to measure. ANAM testing methods could be further advanced with validation against the better-established neurotoxicology models [25]. Current Army initiatives include testing effects of permethrin and JP8, following up on other human and animal studies demonstrating neurocognitive deficits [26, 27]. Mood changes are among the first and most consistent changes with neurotoxicants. The influence of mood state and other additional psychological and environmental stressors on neurotoxicological responses in a military deployment needs to be carefully studied to make practical field tools useful. Table II lists some of the key priorities for development of these health monitoring methods.

**Table II. Examples of Potential Neurotoxicants Relevant to the Military and Occupational
and Post-deployment Health Applications**

- Blast overpressure and combustion gases inside defeated military vehicles and craft*

- Petroleum products*

- Chemical Agent Resistant Coatings, paints, solvents, painting, decontamination

- Combustion products from burning garbage dumps

- Smokes and obscurants

- Insecticides (e.g., permethrin and DEET)

- Agricultural chemicals, especially those banned as harmful in the U.S. (e.g., dieldrin)

- Air quality in closed compartments (e.g., submarines)

- Heavy metals used as armor and armor penetrators (e.g., depleted uranium)*

- Industrial chemical contaminants of high toxicity (e.g., methyl mercury)*

- Mixtures of industrial wastes (possibly including radiological waste)*

- Interactions of toxic chemicals with electromagnetic radiation (e.g., radar systems)

- Interactions of toxic industrial/agricultural chemicals with operational factors (e.g., heat, psychological stress, dust)

- Combustion products of composite materials for lighter weight vehicles and aircraft

Note: *= "Exposure conditions previously studied or currently proposed for study using automated neuropsychological testing"

ANAM was used to evaluate the effects of depleted uranium (DU) in Gulf War veterans with embedded DU shrapnel Although DU is turning out to be a relatively safe heavy metal, uranium distributes to the central nervous system (CNS) and thus further investigation was warranted. The human studies have not revealed any clear effects [28], but this testing application raised issues of repeatability and learning

effects (i e., does the absence of improvement actually reflect a decrement in performance on some tests?), absence of a baseline testing comparison, and other confounding psychological stressors related to the initial traumatic wounding events.

6.4.4 Research challenges

6.4.4.1 Lack of objective testing for mood state

Mood disturbances including increased irritability and depression are prevalent reactions to many of these stressors including, for example, hypoxia [14], neuroglycopenia [13], and a variety of neurotoxicants [24], with resultant changes in motivation to perform well confounding the testing At present, the subjective Profile of Mood States [29] is the primary instrument used in assessing mood status clinically; alternate tests that objectively quantify and distinguish characteristics such as curtness, lassitude, and helplessness from timed responses that also attempt to measure cognitive lapses in speed or accuracy have not yet been produced. Advances in methods to assess mood will be invaluable in neuropsychological evaluations.

6.4.4.2 More data generated than can be productively analyzed

Researchers are drowning in the large volume of data produced by neuropsychological test batteries, with the large number of test options, variations in how the tests are administered, and more outcome variables such as speed and accuracy associated with each test. This seemingly infinite combination of outcome measures complicates interpretation of results, comparability with other studies, and study design, because of the increased likelihood of Type II error. If many of the available tests truly represent different functional axes, then bioinformatic methods being used to interpret genomics data may be needed. Alternatively, the testing could be reduced to five or six key tests with some kind of consensus standards. As an example, Kabat [4] found commonalities in some of the ANAM tests using principal components analyses, identifying three factors: processing speed/efficiency, retention/memory, and working memory. Bleiberg [30] produced similar factors in a separate analysis of data sets from sports concussion studies. Conceivably, one test with the strongest weighting against each factor could be selected as the starting point for an efficient test battery. The ANAM Research Evaluation System (ARES) battery devised to operate on a PDA is an example of a parsimonious starting point, consisting of simple reaction time, math processing, matching to sample, code substitution, memory search, and logical relations.

6.5 GULF WAR ILLNESSES—A MODEL OF POST-DEPLOYMENT NEUROPSYCHOLOGICAL CONCERNS

6.5.1 Post-deployment health concerns

Cognitive status changes important to Soldier performance may also indicate early disease changes. As a result of the 1991 Persian Gulf War, neurological conditions and diseases have acquired specific importance in research on Soldier monitoring and protection. These range from chronic multi-symptom illnesses such as fibromyalgia, chronic fatigue syndrome, and multiple chemical sensitivities, to early indications of neurodegenerative diseases such as Parkinson's Disease (PD) and amyotrophic lateral sclerosis (ALS) [31, 32]. Seemingly every conceivable etiology has been proposed for undiagnosed Gulf War illnesses, but the investigations have narrowed to just a few factors, including Soldier fitness and physical activity that may affect mental outlook and resilience [33], emotional stress influences [31], and specific neurotoxicants [25, 34, 35]. This thrusts neuropsychological testing into a central role in post-deployment

health research.

6.5.2 Neuropsychological complaints

Neuropsychological assessments of Gulf War veterans have been conducted in all of the major veteran study cohorts; unfortunately, only a few investigators have conducted rigorous testing, and most have relied on symptom checklists. Every study has reported greater cognitive complaints for Gulf War veterans who deployed compared to non-deployed veterans, and nearly every study has described associated symptoms of fatigue and depression. For example, based on structured interviews, Iowa veterans who deployed to the Gulf had a higher prevalence of problems with memory and forgetfulness (>20% of respondents) compared to those who had not (6%-8% of non-deployed respondents) [36]. There was a difference in the prevalence, but not in the nature of the complaints, with both deployed and non-deployed veterans reporting difficulty in concentrating and symptoms of depression. These and other studies indicate no unique syndrome or symptom complex, but a higher prevalence of illness in veterans who deployed to the Gulf, probably reflecting a general phenomenon affecting well-being of individuals after involvement in war or other significant events [37, 38].

6.5.3 Poor correlation between neurological symptom complaints and neuropsychological test outcomes

Subjective complaints are not well reflected in neuropsychological testing performances. For example, Gulf War deployed veterans from Oregon and Washington states with undiagnosed illnesses revealed small differences in memory, attention, and response speed on a large battery of tests, but large differences in their psychological complaints compared to a sample of non-deployed veterans [39]. White et al. [40] studied two cohorts of Soldiers who deployed to the Gulf, and compared their responses to a group which was sent to Germany instead of to the Gulf. Detailed testing revealed no statistically significant difference in cognitive functioning, but mood complaints were significantly higher in Gulf War-deployed Soldiers. It was noted that Soldiers who reported that they believed they had been exposed to chemical or biological warfare agents demonstrated poorer performance on several cognitive tests, raising issues about motivation [40, 41]. Differences in cognitive test measures for Gulf War-deployed forces in the British studies disappeared after correction for multiple comparisons and adjustments for depressed mood [42]. Proctor studied the entire cohort of Danish forces deployed just after the end of hostilities in the Gulf and found no differences in detailed neuropsychological testing compared to non-deployed personnel, but did find a higher incidence of mood complaints (fatigue and confusion) [43]. The smallest but most highly studied and reported sample is that of Robert Haley and his colleagues who have focused their attention on 26 sick veterans compared to a similar number of healthy veterans In Haley's sick veterans, intellectual and cognitive function were measurably decreased, but these findings may be confounded by major depressive illness, alcoholism, and post-traumatic stress disorder (PTSD) [44]. Another study that includes detailed neuropsychological testing and objective brain biochemical changes evaluated by magnetic resonance spectroscopy is currently underway with veterans from northern California. These data from various Gulf War cohorts raise an important issue of the influence of mood disturbances on cognitive function testing. It remains an open question about how well these domains can be evaluated in an automated push-button test in patients with fatigue and depression. Future ANAM developments will almost certainly have to consider testing other sensory systems.

6.5.4 New studies in Force Health Protection

The 21-year Millennium Cohort Study initiated in 1999 and now comprising nearly 100,000 service members [45] has neurological health as the highest priority objective. However, there are no sensitive

measures against which to base any associations, and the study must rely on diagnosed disease and subjective reports. The emergence of neurological symptoms and proposed pathophysiology involving psychological or toxicological causes opened the door to consideration of longer-term neurological diseases, especially those with a suspected environmental influence such as ALS and PD. Although data supporting any connection between military service exposures and these diseases is very thin because of the small number of cases and long disease latency, we are still ill equipped to obtain early detection of disease in these individuals. Neuropsychological testing is one important approach being employed in the investigation of Gulf War illnesses and in studies on early detection and monitoring disease progression in PD in Army-sponsored research. It remains to be seen if neuropsychological testing can provide a sensitive indication of neurodegenerative disease changes ahead of functiona. imaging and physiological testing [46].

6.6 CURRENT AND FUTURE DEVELOPMENT OF THE ANAM TOOL

6.6.1 Exploratory efforts

In May 2001, the Army sponsored a reunion of two dozen researchers who had piloted the development of neuropsychological tools under the sponsorship of the late Fred Hegge. Fred Hegge's vision was straightforward; we needed better tools to practically and usefully test brain function. During his tenure as the Director of the OMPAT, and later as the Director of the Military Operational Medicine Research Program, he was generous and insightful in bringing a range of talented scientists into the military neuropsychological testing family and providing enthusiastic mentoring and support to every new idea. This Pensacola reunion kicked off a new series of efforts to develop the ANAM and to coordinate the applications. It was especially important to impose some order on the chaotic mix of software versions and to standardize test procedures to enable comparisons of datasets between experiments. Every new application of ANAM seemed to include new and different test batteries and constant changes in test configurations. The Pensacola presentations recapitulated the lineage of ANAM back to the Walter Reed Performance Assessment Battery that had first automated commonly used neuropsychological tests [47], and concluded with current efforts to standardize the test procedures, software tools, and provide real-time analytic "back ends." The wide diversity of applications highlighted the broad importance of such a testing tool, with studies presented that ranged from Navy diving to radiation exposure by "liquidators" at Chernobyl; attempts to baseline Soldiers and Marines in psychology clinics; and specific applications to head injury, multiple sclerosis, and neurodegenerative diseases such as PD. Unfortunately, few of these studies have been published as full reports in the open literature, in part, because most of these have been opportunistic, with protocols that were not primarily guided by an ANAM-related hypothesis. The stressors and their effects on the individuals have not been well characterized, and the ANAM tests and methods have varied between tests and cannot be readily compared.

6.6.2 The way forward

The ANAM summit meeting led to a commitment by the Military Operational Medicine Research Program to champion the development of a family of standardized ANAM tools and their applications through military research studies, direct support to relevant extramural efforts, and leveraging of relevant grants and Congressional interest funding. This program support has spawned a range of research activities within the past few years The development of the ANAM software has been headed by Kathy Winter (SPAWAR, Pensacola), supported through Army funding related to operational medicine and force health protection

efforts. This effort was guided in part by CDR Dennis Reeves (Camp Pendleton Marine Base), and includes novel efforts by Dr. Tim Elsmore (Activity Research Services, San Diego) in the development of OS language palm version software, supported through a series of competitive Small Business Innovative Research awards. Independent verification and validation of testing procedures, including hardware and software analyses, has been provided for many years by Drs. Robert Schlegel and Kirby Gilliland at the University of Oklahoma, and this center has been licensed to continue ANAM standardization, distribution, and further development for the DoD. Specific applications in concussion studies by Dr. Joe Bleiberg (National Rehabilitation Hospital, Washington, D.C.), and in multiple sclerosis and other veterans disease issues by Dr. Robert Kane (Department of Veterans Affairs, Baltimore) have spearheaded the development of testing procedures and meaningful interpretation of results. Other diverse ANAM applications have ranged from development of drugs for treatment of incapacitating headache by Joe Bleiberg, to improvement of combat helmet designs in parachute training and assessment of head injury and recovery following blast injuries by Dr. Deborah Warden (Defense Veterans Head Injury Program). Dr. Susan Proctor and MAJ James Ness formed a DoD-VA partnership to compare ANAM and other versions of neuropsychological tests in Soldiers stationed in Bosnia, pioneering the use of neuropsychological testing to monitor performance status in deployed forces. Most recently, Dr. Stephen Grate has been instrumental in introducing neuropsychological testing into several key Army grant awards for studies on co-morbidities in PD, notably important studies by Dr. Ken Marek (Institute of Neurodegenerative Disorders, New Haven, CT), and has shepherded the efforts to protect intellectual property rights of the various inventors so that the ANAM tools will remain freely available for government testing and applications.

6.7 CONCLUSION

The diverse military applications of ANAM testing described in this paper represent an ambitious agenda, but this does not imply that a single test battery or methodology is an appropriate fit to all these purposes. ANAM is intended to provide a family of standardized tests that can be translated across platforms, with batteries tailored to the appropriate use. Interpretation of test results will also vary according to the intended application, with very different standards and thresholds applied to epidemiological health screening tools and to individual fitness-for-duty tests. The first proof of the value of the ANAM investment will be any application where an ANAM test battery gains a reputation as a practical standard of testing, with proven predictive or diagnostic value. The most mature application of automated neuropsychological testing to-date has been in neurotoxicology assessments.

Chapter 6 - REFERENCES

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